REMARKS

Claims 22-50 remain active and under consideration.

Applicant wishes to express her sincere gratitude to Examiner Michele Joike for the helpful and courteous discussion conducted with her U.S. representative, Mr. William Beaumont, on February 24, 2009. During that discussion, distinctions between the claimed invention and the cited references were noted. Further to, and consistent with, the remarks made during that discussion, Applicant wishes to make the following remarks below.

REQUEST FOR RECONSIDERATION

Claims 22-25, 31, 33, 38, 41-44, 47 and 50 stand rejected under 35 USC 102(b) as being anticipated by U.S. 2002/0022228.

However, this reference neither discloses nor suggests the claimed subject matter.

Notably, the present invention relates to a method for quantitatively assessing the DNA excision and resynthesis repair capacities of a biological medium. The assay has been designed so as to be as specific as possible to the DNA excision and resynthesis repair capacities of the biological medium being tested. One important aspect of the claimed method is that DNA repair mechanisms associated with strand breaks and nuclease activity are not measured. In order to accomplish this, the claimed method only uses supercoiled DNA, which contains a number of random alterations.

Supercoiled DNA is DNA whose topology has been manipulated so as to comprise more (or sometimes less) than the normal one helical twist per 10.4 base pairs. The term "supercoiled DNA" is a well understood term in the art. See the attached definition of this term in Exhibit A, which is from Biology-Online.org.

Further, supercoiled (also sometimes called super helical) DNA is a specific term and refers to a specific topologically manipulated state of a DNA molecule. DNA is placed into a supercoiled state by a cell using specific enzymes such as topoisomerases and DNA gyrases, which themselves normally use intracellular ATP as the energy source to introduce these alterations into the DNA molecule. See Exhibit A. It is not normally possible for DNA to enter into a supercoiled state without the expenditure of stored intracellular energy as the topological

manipulation of the DNA molecule into a supercoiled state increases the potential energy in the DNA structure and hence consumes energy.

As the target DNA is supercoiled, no DNA strand breaks and/or no nuclease digestion occurrs. DNA strand breaks inherently lead to a relaxation of supercoiled DNA into its base or lowest energy helical structure, as a stand break allows the DNA molecule to attempt to modify its structure so as to remove the additional twists.

Several methods exist to determine whether or not a sample of DNA is in a supercoiled state and also to separate supercoiled DNA from a pool of supercoiled and non-supercoiled DNA. One method widely used by workers in the field is described in the reference "Molecular Cloning: A Laboratory Manual" by J. Sambrook, E.F. Fritsch and T. Maniatis, Cold Spring Harbor N.Y., (1989) and is based upon the observation that supercoiled DNA can be characterized by its electrophoresis migration pattern on an agarose gel. Therefore, one having ordinary skill in the art would have no difficulty in experimentally determining whether or not a DNA sample was supercoiled or not. See Exhibit A.

The examiner's assertion that the DNA used in '228 is supercoiled is, most respectfully, incorrect. In '228, experiments are conducted using short synthesized oligonucleotides ("oligos") (30-40 bp), which contain various features such as base mismatch or apurinic/apyrimidinic sites. Such short oligos inherently are not supercoiled, i.e., the topology of these short oligonucleotides has not been altered using a suitable enzyme as would be required as described above.

The examiner also states that the DNA used in '228 can be a plasmid, but this is also clearly incorrect. Each and all of the experimental examples given in '228, use short single- or double-stranded oligos. In '228, it is disclosed that these single or double stranded oligos can be made from plasmid DNA, for instance by restriction endonuclease digestion of the plasmid to form a small linear double stranded oligonucleotide fragment (see paragraph [00931) subsequent chemical treatment of this fragment yields a suitable lesion which can be acted upon by the repair mechanisms present in the tested biological medium. Plasmid DNA is clearly, not, however used nor is it suggested that it could be used, as the repair target/reagent in '228.

Hence, '228 clearly would not put the artisan in possession of the claimed invention.

Moreover, '228 proposes a different methodology from the claimed invention inasmuch '228 describes the use of short bound single or double stranded oligonucleotides of known

sequence which contain one or more defects such as a base mismatch or apurinic site, mimicking a mutation which requires excision and resynthesis repair. Samples are then applied to the bound oligos and the incorporation of labeled nucleotides is used to determine the repair capacity of the tested sample. The '228 method only measures DNA repair mechanisms which act upon the selected mutations which diminishes detect and record the effects of other repair mechanisms.

The present invention, in contrast, uses altered supercoiled plasmids to test the repair capacities of a biological sample or medium. These altered plasmids are purified so that only supercoiled plasmids are isolated, which means that plasmids which have undergone a strand break or which more generally have a damaged structure (and have probably been acted upon by a nuclease) are eliminated. The remaining supercoiled plasmids which contain a random assortment of other types of mutations and lesions which require DNA excision and resynthesis can, therefore, act as a reagent upon which the excision and resynthesis repair capacities of the biological medium can be measured.

The claimed method is, moreoever, superior to that described in '228. Notably, although the exact mutations/lesions are not known for the mutated supercoiled plasmids of the claimed invention, because the target reagent (the plasmids in claim 22) contain a large number of mutation types in a wide variety of locations, such a heterogeneous target reagent can more accurately quantify all the various excision and resynthesis repair capacities of the biological medium than a target reagent which consists of large numbers of a single mutation type (as in '228).

Clearly, one skilled in the art would not have thought to use supercoiled plasmid DNA as a target reagent as in the claimed invention, but instead would have followed the disclosure of '228 and used a set of short oligos.

Further, the examiner refers to You et al (2005) as disclosing that DNA is normally supercoiled. This reference relates to plasmid DNA which, as previously explained, is supercoiled only by the action of specific enzymes in the bacteria in which the plasmid was propagated. Hence, although this reference teaches that most plasmid DNA is supercoiled, this does not affect the teaching of '228 which uses linear short oligonucleotides which are not supercoiled. Hence, You et al does not support the examiner's arguments that the oligos used in '228 are supercoiled.

Furthermore, attached herewith is an unexecuted Rule 132 Declaration of Dr. Sylvie Sauvaigo. In essence, Dr. Sauvaigo readily distinguishes between 1) the different objectives of the claimed invention and '228, 2) the different methodologies of the claimed invention and '228, and 3) the different results of each.

First, Dr. Sauvaigo notes that '228 provides a method to measure DNA repair mechanisms that act upon selected mutations. In contrast, the claimed invention provides a method for testing the DNA excision and resynthesis properties of a biological sample or medium.

Second, Dr. Sauvaigo observes that '228 uses short bound single- or double-stranded oligonucleotides to measure DNA repair mechanisms of selected mutations, whereas the claimed method uses supercoiled plasmids for testing DNA excision and resynthesis properties of a biological sample.

Third, the results afforded by the claimed method are advantageous over the method of '228 inasmuch as the claimed invention uses a heterogeneous target reagent (supercoiled plasmid DNA) that can accurately quantify all of the various DNA excision and resynthesis repair capacities of a biological medium.

Hence, it is clear that neither '228 alone or in combination with You et al would have anticipated nor rendered obvious the claimed invention at the time the claimed invention was made.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 26-28 stand rejected under 35 USC 103(a) as being unpatentable over US2002/0022228 in further view of Douki et al.

However, Douki et al use calf thymus DNA and therefore the DNA used in Douki et al, is of unknown fragment length, sequence and mutation type/frequency.

Moreover, it is not possible to combine the teaching of '228 and Douki et al, so as to arrive at the subject matter of claim 22 as several essential features are missing from both references, in particular that the target DNA is supercoiled and that the target DNA is a plasmid.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claim 29 stands rejected under 35 USC 103(a) as being unpatentable over US2002/0022228 in further view of Meselson et al.

However, Meselson et al, addresses a different problem, namely the separation of macro-

molecules, such as supercoiled plasmid DNA, using a density gradient. No combination of '228 and Meselson et al, could be made to arrive at the subject matter of claim 22, as Meselson et al, although disclosing supercoiled plasmid DNA *per se,* does not describe that it could be used in a method to quantify the excision and resynthesis DNA repair capabilities of a biological medium.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 34-36 stand rejected under 35 USC 103(a) as being unpatentable over US2002/0022228 in further view of Chiu et al.

However, Chiu et al, relates to a different problem, namely improved adhesion of DNA to a microarray slide and as a consequence better DNA hybridisation and detection. Chiu et al would have failed to correct the deficiencies of '288 inasmuch as Chiu et al use synthesised oligonucleotides which inherently are not supercoiled for the reasons given above.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 32 and 37 stand rejected under 35 USC 103(a) as being unpatentable over US2002/0022228 in further view of Zierdt et al.

However, Zierdt et al, relates to a different problem, namely particle retention on large pore filters, in particular cellulose nitrate filters. The retained particles include bacteria, human blood cells and polystyrene spheres.

Clearly, Zierdt et al fails to correct the deficiencies of '228.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 39 and 40 stand rejected under 35 USC 103(a) as being unpatentable over US2002/0022228 in further view of Gelfand et al.

However, Gelfand et al, use short oligonucleotides, hence this reference would have also failed to correct the deficiencies of '228 for the reasons noted above.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 39 and 40 stand rejected under 35 USC 103(a) as being unpatentable over US2002/0022228 in further view of Yershov et al.

However, Yershov et al, use short oligonucleotides, therefore this reference also fails to correct the deficiencies of '288.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Claims 39 and 40 stand rejected under 35 USC 103(a) as being unpatentable over

US2002/0022228 in further view of Randerath et al.

Randerath et al, disclose the use of calf thymus DNA and, therefore, the DNA used in this method is of unknown fragment length, sequence and mutation type/frequency.

However, this reference clearly fails to correct the deficiencies of '228.

Hence, this ground of rejection is unsustainable and should be withdrawn.

Applicant also wishes to address the examiner's comments regarding MPEP 2144.05 and the two citations thereof in the Official Action of September 4, 2008.

Specifically, it is not possible to include the claimed feature that the DNA target is supercoiled into the disclosure of '228 as this feature is not an obvious alternative which can be taken from other methods of the cited references arguably used for similar purposes in the art. In particular, none of the cited references discloses or suggests the exclusive use of supercoiled plasmid DNA for any reason. In addition, it may not even be possible to supercoil the small oligonucleotides used in '228 as such small oligos would be unlikely to act as a good substrate for an enzyme such as a DNA gyrase or topoisomerase. Of course, '228 neither discloses or suggests even attempting to supercoil the small oligos used therein in any event. Finally, there would be no reason to supercoil the oligonucletotides used in '228, of course, as the inventors of '228 would have surely known that the short oligonucleotides used would not have suffered a strand break or nuclease digestion.

Hence, the citation of MPEP 2144.05 to support the above claimed rejections is unsustainable and should be withdrawn.

As noted above, the use of supercoiled plasmid targets as an element of the present invention allows the claimed method to disregard the effects of DNA strand breaks and nuclease action. In discounting the effects of repair mechanisms acting to correct strand breaks and/or nuclease activity, the claimed method allows for a quantitative assessment to be made of only the DNA excision and resynthesis properties of a biological medium being tested. Such a method is, moreover, clearly advantageous as compared to the method of '228 as the heterogeneity of the repair targets in the claimed method allows all the various DNA excision and resynthesis repair properties of the medium being tested to be quantified. These aspects are also neither disclosed nor suggested in the art of record.

Thus, it is clear that none of the references of record, either alone or in combination, would have either anticipated or rendered obvious the claimed invention to one skilled in the art

at the time the claimed invention was made.

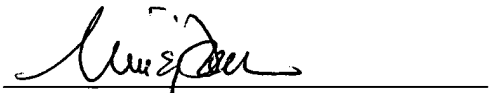
An executed version of Dr. Sauvaigo's Rule 132 Declaration will be forwarded immediately upon receipt. Receipt is imminently expected.

No additional claims fees are due.

Accordingly, in view of all of the above, it is believed that the present application now stands in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

THE NATH LAW GROUP



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